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(54) Title: BIO-COMPATIBLE POLYMERIC MATERIALS

(57) **Abstract:** A bio-compatible polymeric material for use in medical applications, for example in an orthopaedic implant, comprises a copolymer having a unit A in combination with a unit B and/or a unit C, wherein bio-compatible moieties are associated with said copolymer and A represents a semi-crystalline polyaryletherketone moiety (especially polyetheretherketone), B represents a unit which is incompatible with unit A (e.g. polydimethylsiloxane) and C represents an amorphous polyaryletherketone or polyarylethersulphone unit. Methods for preparing, methods of using and devices incorporating the polymeric material are also described.

BIO-COMPATIBLE POLYMERIC MATERIALS

This invention relates to bio-compatible polymeric materials and particularly, although not exclusively, provides a bio-compatible polymeric material, a method of producing and the use of such a material in medical treatment, for example in a prosthesis.

Much research is being directed to the provision of materials to meet the growing need for prosthetic devices such as orthopaedic, dental or maxillofacial implants. For example, nearly half a million patients receive bone implants each year in the US with the majority being artificial hip and knee joints made from titanium or colbalt-chrome alloys. However, these materials are too stiff leading to bone resorption, loosening of the implant and, consequently, have lifetimes of less than 10 years. Additionally, medical devices or prostheses such as pacemakers, vascular grafts, stents, heart valves, catheters and dental implants that contact body tissues or fluids of living persons or animals have been developed and used clinically.

A major problem with medical devices such as those described is the susceptibility to foreign body reaction and possible rejection. Consequently, it is of great interest to the medical industry to develop materials from which medical devices can be made which are less prone to adverse biological reactions that typically accompany introduction of medical devices into humans or animals.

It is an object of the present invention to address the above described problems.

According to a first aspect of the present invention, there is provided a bio-compatible polymeric material for use in medical applications, wherein said material comprises a copolymer comprising a unit A in combination with a unit B and/or a unit C, wherein bio-compatible moieties are associated with said copolymer and A represents a semi-crystalline polyaryletherketone moiety, B represents a unit which is incompatible with unit A and C represents an amorphous polyaryletherketone or polyarylethersulphone unit.

Suitably, B units are sufficiently chemically dissimilar to A units, such that blocks of B units selectively aggregate when the copolymer is cooled from the melt.

In the scientific literature there is inconsistency in the use of descriptions such as "bio-compatible", "bio-active" and "bio-materials". In the context of the present specification, the term "bio-compatible" has generally been used to refer to a material which is compatible with use in medical applications, for example by not being toxic or otherwise harmful to living materials. It also encompasses materials which have a biological or physiological effect when associated with living materials.

"Bio-compatible moieties" referred to herein suitably refer to moieties which are compatible with use in medical applications, for example by not being toxic or otherwise harmful to living material. Such bio-compatible moieties may be arranged to bond (for example to form ionic or covalent bonds) or otherwise interact with materials

present in human or animal bodies in order to improve their integration and acceptance by such bodies.

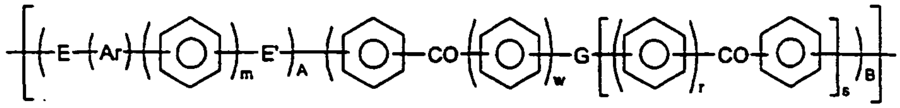
Preferably, said bio-compatible polymeric material has improved or enhanced bio-compatibility compared to said copolymer in the absence of associated bio-compatible moieties.

Bio-compatible moieties suitably include moieties arranged to reduce adverse biological reactions when the copolymeric material is introduced into (or otherwise associated with) a human or animal body. For example, adverse biological reactions associated with introduction into a human or animal body of said copolymer having said bio-compatible moieties may be less compared to use of the same copolymer but which does not include associated bio-compatible moieties. Furthermore, said bio-compatible material preferably has greater bio-compatibility than a polymer comprising units of A alone.

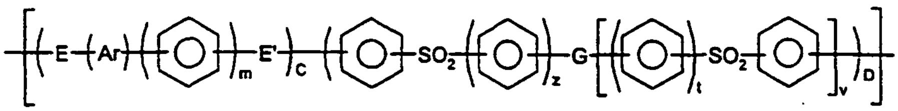
Preferably, bio-compatible moieties are associated with at least one of either unit B or unit C of said copolymer.

Said unit A preferably includes aromatic group containing moieties linked by -CO- and/or -Q- groups, where Q is an oxygen or sulphur atom. Unit A preferably does not include $-SO_2-$ groups since such would tend to render the unit amorphous.

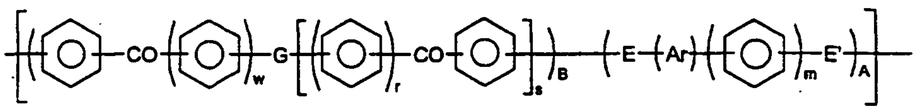
Unit A may include a first unit which is of general formula

 IV

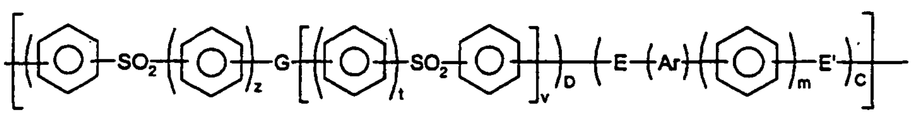
or of general formula

 V

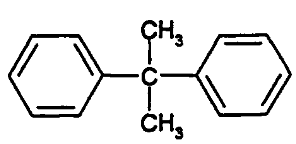
or of general formula

 IV*

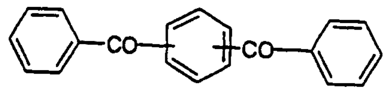
or of general formula

 V*

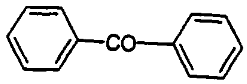
provided said unit is semi-crystalline, wherein the phenyl moieties in units IV, IV*, V and V* are independently optionally substituted, wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**, and (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

(i)** 

(i)*



(i)



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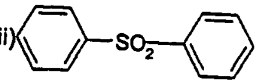

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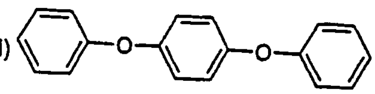

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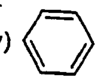

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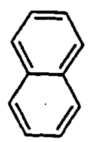

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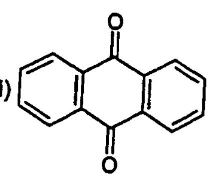

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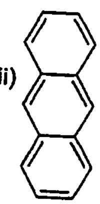
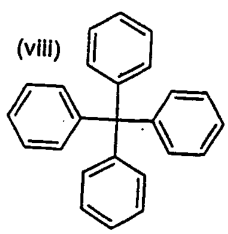
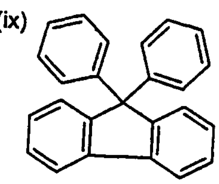


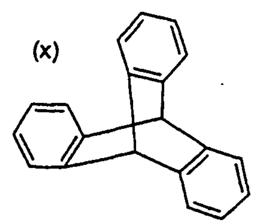
(viii)



(ix)



(x)



Unless otherwise stated in this specification, a phenyl moiety may have 1,4- or 1,3-, especially 1,4-, linkages to moieties to which it is bonded.

Where a phenyl moiety described herein is optionally substituted, it may be optionally substituted by one or more halogen, especially fluorine and chlorine, atoms or alkyl, cycloalkyl or phenyl groups. Preferred alkyl groups are C_{1-10}, especially C_{1-4}, alkyl groups. Preferred

cycloalkyl groups include cyclohexyl and multicyclic groups, for example adamantyl.

Another group of optional substituents of a phenyl moiety comprises alkyls, halogens, C_yF_{2y+1} where y is an integer greater than zero, O-R^q (where R^q is selected from the group consisting of alkyls, perfluoralkyls and aryls), $CF=CF_2$, CN, NO_2 and OH. Trifluormethylated phenyl moieties may be preferred in some circumstances.

Preferably, said phenyl moieties are not optionally-substituted as described.

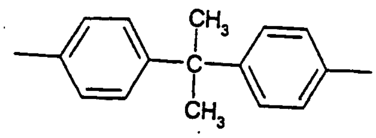
Where w and/or z is/are greater than zero, the respective phenylene moieties may independently have 1,4- or 1,3-linkages to the other moieties in the repeat units of formulae II and/or III. Preferably, said phenylene moieties have 1,4- linkages.

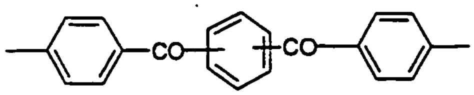
Preferably, the polymeric chain of the copolymer does not include a -S- moiety. Preferably, G represents a direct link.

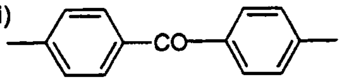
Preferably, m is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, r is in the range 0-3, more preferably 0-2, especially 0-1. Preferably t is in the range 0-3, more preferably 0-2, especially 0-1. Preferably, s is 0 or 1. Preferably v is 0 or 1. Preferably, w is 0 or 1. Preferably z is 0 or 1

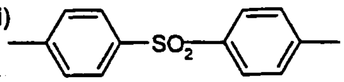
Preferably Ar is selected from the following moieties (xi)* (xi)**, and (xi) to (xxi):

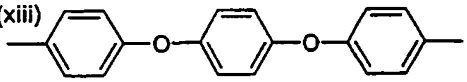
(xi)**

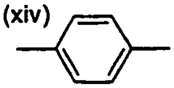


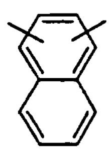
(xi)* 

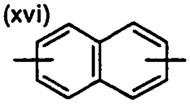
(xi) 

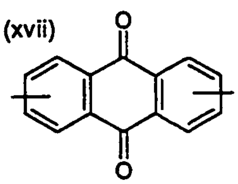
(xii) 

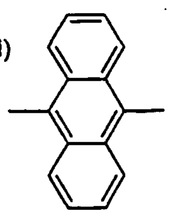
(xiii) 

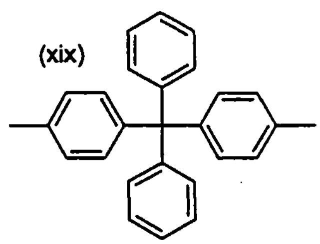
(xiv) 

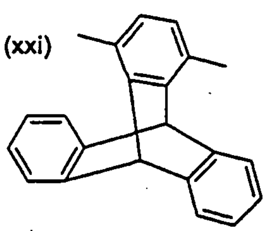
(xv) 

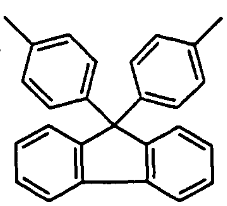
(xvi) 

(xvii) 

(xviii) 

(xix) 

(xxi) 

(xx) 

In (xi)*, the middle phenyl may be 1,4- or 1,3-substituted.

Preferably, (xv) is selected from a 1,2-, 1,3-, or a 1,5- moiety; (xvi) is selected from a 1,6-, 2,3-, 2,6- or a 2,7- moiety; and (xvii) is selected from a 1,2-, 1,4-, 1,5-, 1,8- or a 2,6- moiety.

Said unit A may include a semi-crystalline unit which is of general formula IV or IV* as described above, provided said unit is crystallisable. Suitably, to be crystallisable, said unit A does not include any Ar group of formula (i)**, (ii), (viii), (ix) or (x). More preferably, it may also not include an Ar group of formula (v), (vi) or (vii). Preferred Ar groups consist of one or more phenyl groups in combination with one or more carbonyl and/or ether groups.

Said unit A preferably includes only unsubstituted phenyl moieties, ether moieties and ketone moieties. That is, unit A preferably does not include repeat units which include -S-, $-SO_2-$ or aromatic groups other than phenyl. Preferred units A include:

(a) units of formula IV wherein Ar represents moiety (iv), E and E' represent oxygen atoms, m represents 0, w represents 1, G represents a direct link, s represents 0, and A and B represent 1 (i.e. polyetheretherketone).

(b) units of formula IV wherein E represents an oxygen atom, E' represents a direct link, Ar represents a moiety of structure (i), m represents 0, A

represents 1, B represents 0 (i.e. polyetherketone);

(c) units of formula IV wherein E represents an oxygen atom, Ar represents moiety (i)*, m represents 0, E' represents a direct link, A represents 1, B represents 0, (i.e. polyetherketoneketone).

(d) units of formula IV wherein Ar represents moiety (i), E and E' represent oxygen atoms, G represents a direct link, m represents 0, w represents 1, r represents 0, s represents 1 and A and B represent 1. (i.e. polyetherketoneetherketoneketone).

(e) units of formula IV, wherein Ar represents moiety (iv), E and E' represents oxygen atoms, G represents a direct link, m represents 0, w represents 0, s, r, A and B represent 1 (i.e. polyetheretherketoneketone).

Of the aforesaid, the polymers described in (a) and (b) are preferred, with the polymer described in (a) being especially preferred.

The existence and/or extent of crystallinity in a polymer is preferably measured by wide angle X-ray diffraction, for example as described by Blundell and Osborn (Polymer 24, 953, 1983). Alternatively, crystallinity may be assessed by Differential Scanning Calorimetry (DSC).

Unit B may represent any unit which is incompatible with unit A and, to this end, B preferably includes fewer,

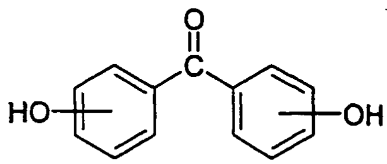
suitably less than half or even a quarter of the number of ether moieties in unit A; suitably fewer, suitably less than half or even a quarter of the number of ketone moieties in unit A; and suitably fewer, suitably less than half or even a quarter of the number of phenyl moieties in unit A. Unit B preferably does not include any ether moieties in its backbone. Preferably, it also does not include any ketone moieties in its backbone and, more preferably, does not include any phenyl moieties in its backbone. An example of a unit B is a dimethylsiloxane, especially a polydimethylsiloxane, moiety.

Where B represents a unit which is bio-compatible, it may represent a unit which has a greater bio-compatibility than repeat unit A. An example is the aforementioned polydimethylsiloxane.

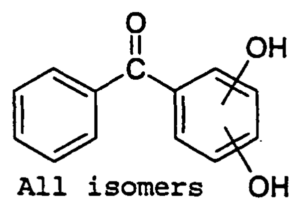
Said unit C preferably includes aromatic group containing moieties linked by $-SO_2-$ and/or -CO- and/or -Q- groups, where Q is as described above provided, however, that said third unit suitably includes a means to render it amorphous (hereinafter said "amorphous means") and/or not crystallisable with polyarylether ketones or polyarylthioether ketones and/or not crystallisable with unit A described above.

Said unit C may comprise a unit which is of formula -Q-Z-Q- wherein Z represents said aromatic group containing moiety, wherein said unit is not symmetrical about an imaginary line which passes through the two -Q- moieties provided, however, that said unit is not dihydroxybenzophenone substituted by groups Q at the 4- and 4'- positions (since such a benzophenone acts in the

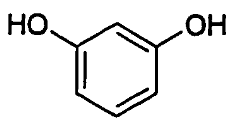
manner of a symmetrical moiety by virtue of the carbonyl group being substantially similar to an ether group thereby allowing the carbonyl group to be interchanged with an ether group in a polyaryletherketone crystal lattice). Said unit C, for example moiety Z, may include a bulky group. Said unit C, for example moiety Z, may include one of the following moieties:

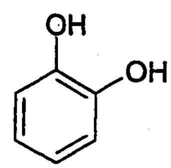


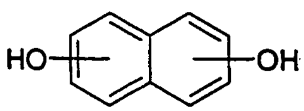
All isomers but not 4,4'-isomer



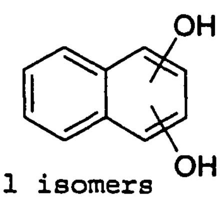
All isomers



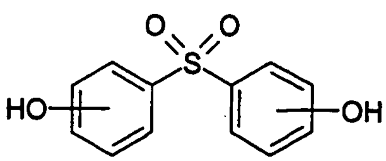




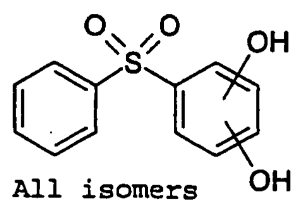
All isomers



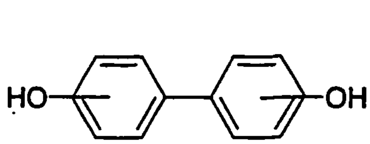
All isomers



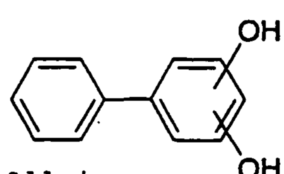
All isomers
- includes 4,4'-isomer



All isomers



All isomers but not 4,4'-isomer



All isomers

Said copolymer may be a random or block copolymer. It may include one or a plurality of units A (which may be identical but are more likely to be different, for example in terms of length and/or structure, whilst still being semi-crystalline as described); one or a plurality of units B (which may be identical but are more likely to be different, for example in terms of length and/or structure, whilst still being incompatible as described) and/or one or a plurality of units C (which may be identical but are more likely to be different, for example in terms of length and/or structure, whilst still being amorphous as described).

Said copolymer may have a structure selected from one of the following structures:

(I)	A-B-A
(II)	A-B-A-B-A
(III)	A-[A-B]$_n$-B
(IV)	A-C-A
(V)	A-B-C-A
(VI)	A-B-A-C-A
(VII)	A-[A-C]$_n$-A
(VIII)	A-[A-B]$_n$-A
(IX)	A-[C-B]$_n$-A
(X)	A-[A-C]-B
(XI)	A-[C-B]$_n$-B
(XII)	A-[ABC]$_n$-A

wherein n represents an integer, for example in the range 1 to 100.

It should be appreciated that where more than one unit A, B and C is included in one of the above structures, one A, B or C in a structure need not be identical in terms of length and/or structure as another A, B or C in the same structure.

Preferably, an end unit of said copolymer (i.e. a unit at the end of the polymer chain of the copolymer) is an A unit. A unit at an opposite end of the polymer chain may be an A or B unit, especially an A unit. Preferably, the number of A units in said copolymer is equal to or greater than the number of B units. More preferably, the number of A units is greater than the number of B units. The sum of the chain length(s) of A units in said copolymer is preferably greater than the sum of the chain length(s) of B units in the polymer. Preferably, a C unit is not present at the end of a polymer chain. Preferably, the number of A units in said copolymer is equal to or greater than the number of C units. More preferably, the number of A units is greater than the number of C units. The sum of the chain length(s) of A units in said copolymer is preferably greater than the sum of the chain length(s) of C units in said polymer.

Said bio-compatible polymeric material may comprise a blend. Said blend may include a polymer or copolymer of units IV, V, IV* and/or V* and, more preferably, includes a semi-crystalline polymer or copolymer which comprises units IV, V, IV* and/or V*. Preferred polyaryletherketones are polymers consisting essentially of units (a), (b), (c), (d) or (e) described above (i.e. polyetheretherketone, polyetherketone, polyetherketoneketone, polyetherketoneetherketoneketone

and polyetheretherketoneketone) together with said copolymer. Said blend preferably includes a polyaryletherketone together with said copolymer and, of these, polyetheretherketone and polyetherketone are preferred and polyetheretherketone is especially preferred. 1 - 50wt% of said polyaryletherketone may be included in a said blend.

Said bio-compatible material may include one or more fillers for providing desired properties. Said bio-compatible material preferably incorporates an X-ray contrast medium. Fillers and/or said X-ray contrast medium is/are preferably distributed substantially uniformly throughout said bio-compatible material.

Where an X-ray contrast medium is provided it suitably comprises less than 25wt%, preferably less than 20wt%, more preferably less than 15wt%, especially less than 10wt% of said bio-compatible material. Where it is provided, at least 2wt% may be included. Preferred X-ray contrast mediums are particulate and preferably are inorganic. They preferably have low solubility in body fluids. They preferably also have a sufficient density compared to that of the polymeric material(s) in said bio-compatible material to create an image if the bio-compatible material is X-ray imaged. Barium sulphate and zirconium oxide are examples of X-ray contrast media. Said particulate material is suitably physically held in position by entrapment within the bio-compatible material.

A said bio-compatible moiety may be selected from an anticoagulant agent such as heparin and heparin sulfate, an antithrombotic agent, a clotting agent, a platelet

agent, an anti-inflammatory agent, an antibody, an antigen, an immunoglobulin, a defence agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a blood agent, a regulatory agent, a transport agent, a fibrous agent, a protein such as avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein and a cell attachment protein, a peptide such as a glycopeptide, a structural peptide, a membrane peptide and a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, an antibacterial agent, an antimicrobial agent such as pencillin, ticarcillin, carbenicillin, ampicillin, oxacillian, cefazolin, bacitracin, cephalosporin, cephalothin, cefuroxime, cefoxitin, norfloxacin, perfloxacin and sulfadiazine, hyaluronic acid, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a nucleotide, a polynucleotide, a nucleoside, a lectin, a ligand and a dye (which acts as a biological ligand), a radioisotope, a chelated radioisotope, a chelated metal, a metal salt, a sulphonic acid or salt thereof, a steroid, a non-steriod, a non-steroidal anti-inflammatory, an analgesic, an anti-histamine, a receptor binding agent, a chemotherapeutic agent, a hydrophilic polymer. (e.g. poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), ethylene oxide-propylene oxide block co-polymers, poly(N-vinyl-2-pyrrolidone) (PNVP), poly(2-hydroxyethyl methacrylate) (pHEMA), HEMA co-polymers, poly(vinyl alcohol) (PVA), polyacrylamide, its derivatives, poly(methyl methacrylate) (PMMA), suitably having a PEG chain on each of the side groups, polysiloxanes (e.g. polydimethylsiloxanes (PDMS)), ionic water-soluble polymers like poly(acrylic acid) (PAAc)) and a polyurethane. Examples of some of the

aforesaid are provided in US5958430, US5925552, US5278063 and US5330911 and the contents of the aforementioned specifications are incorporated herein by reference.

In one embodiment, said bio-compatible moieties may comprise bone morphogenic protein (BMP) as described in US4563489 and patents cited therein and the contents of the aforesaid are incorporated herein. Said BMP may be provided in combination, for example in admixture, with a physiologically acceptable biodegradable organic polymer and said biodegradable polymer may be associated with ends of said polymer of said bio-compatible polymeric material, for example by being covalently bonded to end groups. Thus, in this case, the combination of said biodegradable polymer and BMP defines said bio-compatible moieties. Said biodegradable polymer is preferably a biodegradable polylactic acid; or alternatively, other physiologically acceptable biodegradable organic polymers which are structurally equivalent to polylactic acid can be used as the delivery system for BMP. Examples include poly(hydroxy organic carboxylic acids) e.g. poly(hydroxy aliphatic carboxylic acids), polyglycollic acid, polyglactin, polyglactic acid and poly adonic acids.

Linking moieties, for example linking atoms or groups may extend between repeat units of the copolymer, especially in units B and/or C thereof, and said bio-compatible moieties. Said linking moieties may be covalently bonded to respective repeat units of the copolymer. Said linking moieties may be covalently bonded to said bio-compatible moieties or may otherwise be associated with said moieties.

A said linking moiety may be associated with a single bio-compatible moiety or, alternatively, a said linking moiety may be associated with more than one bio-compatible moiety. Thus, said linking moiety may be mono-functional or multi-functional, for association with one or more bio-compatible moieties. Multi-functional linking moieties may be able advantageously to be associated with more bio-compatible moieties and may, therefore, provide a means to increase the concentration of bio-compatible moieties associated with said copolymer.

Whilst said bio-compatible moieties may be associated with said copolymer by any suitable means, for example covalent bond(s), hydrogen bond(s), encapsulation in a matrix which is bonded to or otherwise interacts with said copolymer, or ionic interaction(s), it is preferred that there are covalent bonds between the bio-compatible moieties and said copolymer or there are ionic interactions between said bio-compatible moieties and said copolymer.

According to a second aspect of the present invention, there is provided a method of preparing a bio-compatible polymeric material, the method including the step of preparing a copolymer comprising a unit A in combination with a unit B and/or with a unit C and optionally including the step of associating a bio-compatible moiety with the copolymer or, when said optional step is not undertaken, selecting at least one unit B or C which is itself bio-compatible, wherein A, B and C are as described according to said first aspect.

Preferably, the copolymer made in the method (prior to the optional step of associating bio-compatible moieties with the polymer) is thermally stable at at least 350°C, suitably thereby to allow thermal processing operations, for example injection moulding, extrusion and/or thermal spraying, without degradation. Furthermore, said copolymer is preferably hydrolytically stable, suitably such that it may withstand long term aqueous contact that may result in use, for example when implanted in a human or animal body. However, in some cases, the copolymer may not be hydrolytically stable until after bio-compatible moieties have been associated therewith.

Preferably, units B and/or C in the bio-compatible polymeric material include associated bio-compatible moieties or are themselves bio-compatible, preferably to a greater extent than units A. Thus, preferably, units A (in combination with any pendent moieties associated therewith) in the bio-compatible polymeric material have a lower bio-compatibility than other units in the material and preferably do not include associated, for example pendent, bio-compatible moieties. By focussing functionalities which are arranged to provide bio-compatibility on units B and/or C, unit A need not be functionalised. This may be advantageous since units B and/or C may be easier and/or cheaper to render bio-compatible compared to unit A which by virtue of its crystalline nature and/or relative inertness, may be more difficult to functionalise such that bio-compatible moieties may be associated therewith. Furthermore, functionalistion of unit A would tend to disrupt the semi-crystalline nature of the unit. Thus, preferably in the method, the crystallinity of A is preserved and is,

therefore, preferably present in said bio-compatible material prepared in the method.

In a first specific embodiment, a copolymer is prepared comprising units A and B wherein unit B includes pendent moieties with associated bio-compatible moieties. The method may involve preparing a copolymer using a first monomer (which provides part of unit B) having a pendent functional group. Said functional group is preferably pendent from an aryl, especially a phenyl, group and may be, for example, a -CN group. The copolymer prepared suitably includes said pendent functional group which may then be treated to allow bio-compatible moieties to be associated with unit B. For example, a said -CN group may be hydrolysed to an acid group which may then be treated with a peptide, as described in Example Ic hereinafter. The method of preparing said copolymer may comprise polycondensing said first monomer with a second monomer (which provides part of unit A) and a third monomer (which provides parts of both units A and B). This may result in a random co-polymer. The method could be adapted to prepare a block copolymer if required. Thus, it should be appreciated that B units are selected in the method to have functionalities that allow efficient and cost-effective attachment of bio-compatible moieties. A specific example of said first embodiment is provided in Examples Ia-c.

In a second specific embodiment, a copolymer is prepared comprising units A and B wherein unit B is itself bio-compatible, suitably in the sense that it has a higher inherent bio-compatibility compared to unit A. The method may involve preparing a copolymer using a first monomer

(which provides part of unit A) and a second monomer (which provides part of unit B), wherein said second monomer is preferably inherently bio-compatible as described. Said first and second monomers are preferably polycondensed. It is preferred that said first monomer is in fact a difunctional polymer, for example hydroxy-terminated polyetherether ketone, and said second monomer is a polymer arranged to be condensed with said polymer. Said second monomer may be polydimethylsiloxane. Thus, preferably, in said second embodiment, a block copolymer is formed. A specific example of said second embodiment is provided in Examples II a and b.

In a third embodiment, the problem of functionalising semi-crystalline polyaryletherketone moieties is addressed. In the embodiment, a copolymer is prepared which includes units A and C wherein units C are preferably more easily functionalised compared to units A so that bio-compatible moieties can be associated with functionalised units C. In view of the amorphous nature of units C, functional groups thereof may be more accessible and, therefore, more easily functionalised. Units C can be functionalised, for example, by electrophilic substitution reactions of aromatic rings, such as by sulphonation, chlorosulphonation, nitration, acylation, halogenation, chloromethylation, phosphonylation, lithiation and (optionally-substituted) alkylation reactions.

In a fourth specific embodiment, a copolymer is prepared comprising units A, B and C. Units B may optionally provide bio-compatibility as described according to the first and second embodiments; and unit C

may optionally provide bio-compatibility as described according to the third embodiment provided that at least one of B and C provides bio-compatibility. Bio-compatible moieties associated with B and C may be the same or different. The polymer can contain A, B and C units that are either dispersed throughout the bulk of the material or in phase domains. For example, where a unit of A, B and/or C defines a relatively small block it may be dispersed; whereas where a block is relatively large domains will be defined. In some cases domains in the size range 0.5 to 400 μm may be formed.

In a fifth specific embodiment, a blend is prepared comprising a first copolymer which comprises units A and B and a second copolymer which comprises units A and C. Units B may optionally provide bio-compatibility as described according to the first or second embodiments; and units C may optionally provide bio-compatibility as described according to the third embodiment, provided that at least one of B and C provides bio-compatibility. The components of the blend may be selected such that there is a tendency for one of the copolymers in the blend to separate from the other copolymer and migrate to a surface of a solid material made from the polymers. Migration may occur during a thermal treatment of the blend. Preferably, the components of the blend are selected such that a copolymer which migrates to the surface includes an associated bio-compatible moiety (especially wherein one of the units of the copolymer is bio-compatible) or is arranged to be functionalised for association with bio-compatible moieties. A specific example of the fifth embodiment is provided in Examples Va-c.

In general terms, the method of the second aspect preferably includes providing said copolymer as part of a solid material. To this end, preferably, a polymeric material which includes said copolymer is formed into a solid. The polymeric material may include said copolymer in combination with one or more other copolymers and/or polymers and/or with other materials, for example fillers, e.g. such as an X-ray contrast medium as described herein. The components of the polymeric material are preferably heated together, suitably at a temperature of at least 200°C, preferably at least 250°C, more preferably at least 300°C, especially at least 350°C, and formed into a desired shape. After formation of the desired shape, moieties, especially units B and/or C, are preferably available at the surface for providing bio-compatibility (e.g. where B and/or C are themselves bio-compatible) and/or for association with a bio-compatible moiety.

When in the desired shape, the polymeric material may define a homogenous mixture of the components thereof so that the concentration of respective components of the polymeric material at the surface is the same as in the bulk. However, preferably, the copolymer and/or the polymeric material is such that the concentration of units B and/or C at the surface is greater than in the bulk -that is units B and/or C tend to migrate to the surface, suitably during thermal processing of the polymeric material.

In a first general embodiment, said polymeric material may include a copolymer of structure A-B-A, suitably as the only organic copolymer and/or organic polymer present. After thermal processing it is found that the units B in

the copolymer tend to phase separate from units A and surface bloom, suitably so that the concentration of B units at the surface is greater than would be expected if units B were uniformly or homogenously distributed throughout the solid. Similarly, if said polymeric material comprises a copolymer of structure A-[A-B]$_n$-B there is surface blooming of units B; if it comprises a copolymer of structure A-C-A there is surface blooming of units C; and if it comprises a copolymer of structure A-B-C-A there can be surface blooming of both units B and C. Thus, in each case, the concentration of units B and/or C at the surface of the solid is greater than expected. Units B and/or C at the surface are then available for association with bio-compatible moieties.

In a second general embodiment, said polymeric material may include a copolymer of a type described according to said first aspect in combination with an additional polymer or an additional copolymer. Said additional polymer or copolymer may include a polymer or copolymer of units IV, V, IV* and/or V* described above with reference to the first aspect and, more preferably, includes a semi-crystalline polymer or copolymer which comprises units IV, V, IV* and/or V*. A preferred additional polymer or copolymer is a polyaryletherketone which may consist essentially of units (a), (b), (c), (d) or (e) described above (i.e. polyetheretherketone, polyetherketone, polyetherketoneketone, polyetherketoneetherketoneketone and polyetheretherketoneketone) and, of these polyetheretherketone and polyetherketone, especially polyetheretherketone, is/are preferred. Where said polymeric material includes an additional polymer and/or

copolymer, the copolymer and additional polymer and/or copolymer are selected so that there is a tendency for the copolymer (or parts thereof) to move away from the additional polymer and/or copolymer, suitably during thermal processing, and migrate towards the surface of the solid, suitably so that there is a greater concentration of units B and/or C of said copolymer at the surface compared to if the copolymer was homogenously dispersed throughout the solid. Thus, again, units B and/or C are available for association with bio-compatible moieties.

In one preferred example of said second general embodiment, said polymeric material includes a copolymer which includes units A and B together with a copolymer which includes units A and C. Suitably one of the copolymers (especially that which includes units A and B) will be arranged to predominantly migrate to the surface. In another preferred example of said second general embodiment, said polymeric material includes a copolymer which includes units A and B together with a homopolymer which includes and, preferably, consists essentially of, units A. The copolymer suitably predominantly migrates to the surface.

The moieties, especially units B and/or C, available at the surface immediately after thermal processing of the polymeric material may: already include functional groups (hereinafter "FG") which can be functionalised to enable association with bio-compatible moieties (the aforesaid first specific embodiment illustrates this); already include functional groups (FG) which are in themselves bio-compatible; comprise units B and/or C which is/are in themselves bio-compatible (the aforesaid second specific

embodiment illustrates this); or may include moieties (e.g. aryl groups) which can be functionalised (e.g. in electrophilic substitution reactions described above) to provide functional groups FG (the aforesaid third embodiment illustrates this).

FG may include a functional group selected from the following: -OH, -CHO, $-NR^{10}_2$, preferably $-NH_2$ or $-NHR^{10}$, -SH, $-CONH_2$, $-CONHR^{10}$, -COOH, -COCl or $-COOR^{10}$ group, a halogen atom, especially a fluorine, chlorine, bromine or iodine atom, $-NO_2$, $-SO_3M$, $-SO_2R^{11}$, $-SO_2NHR^{10}$, $-SO_2NR^{10}_2$ or -COOM groups, an anhydride, an epoxide, a cyanate, -CN, an isocyanate, a carbon-carbon double bond, for example a group $-CR^{10}=CR^{10}_2$ or a (C_o-C_{10}alk) acrylate (wherein "alk" refers to an alkyl group) such as $-COOC(CH_3)CH_2$ and $-COOCHCH_2$, a carbon-carbon triple bond, for example a group $-CR^{10}$ or an azide, wherein R^{10} represents a hydrogen atom or an optionally substituted alkyl group, wherein M represents a hydrogen atom or an alkali metal and R^{11} represents a halogen, especially a chlorine, atom.

Preferred functional groups FG may be selected from the following:- -OH, $-NR^{10}_2$, $-N=CR^{10}_2$, $-OR^{10}$, a halogen, especially a fluorine or chlorine atom, $-NO_2$, -CN and -SO_3M^1 wherein R^{10} represents a hydrogen atom or an optionally-substituted alkyl group and M represents an alkali metal.

The moieties, especially units B and/or C including functional groups FG, available at the surface may, optionally, be further functionalised, for example to provide linking moieties as described above, and then

treated with a material (hereinafter "BCM material") for providing a bio-compatible moiety for association with the copolymer. BCM material may react and/or become associated with functional groups of said copolymer, preferably with functional groups FG as described herein. In one embodiment, BCM material may be arranged to associate a polyurethane with said copolymer. For example, said copolymer may include hydroxy groups and said BCM material provides a diisocyanate and a diol; or said copolymer may include isocyanate groups and said BCM material provides a diisocyanate and a diol. In both cases, said BCM material may be provided by two different compounds.

According to a third aspect of the present invention, there is provided a method of making a medical device or part thereof, the method including the step of forming a layer of a bio-compatible polymeric material on the outside of a support material, wherein said bio-compatible polymeric material is as described according to said first aspect or is made as described according to said second aspect.

Said support material could comprise the same copolymer which is included in the layer of bio-compatible material, suitably before any subsequent treatment to associate it with bio-compatible moieties. In this event, the method may include forming a polymeric material which includes said copolymer into a shape which represents or is a precursor of a medical device or part thereof. Formation into a shape may use any suitably method, for example moulding, machining of a blank, extrusion or the like. Then, the surface of said shape is suitably

treated, for example to functionalise it and/or associate bio-compatible moieties with it.

Preferably, however, said support material is made out of a material which is different to that of the material of the layer of bio-compatible material, suitably before any subsequent treatment to associate it with bio-compatible moieties. Said support material may be made out of any suitable material, for example of a metal, or a plastics material. Preferably, however, said support material comprises a polymer which preferably includes a moiety of formula I and/or a moiety of formula II and/or a moiety of formula III as described above.

In this case, the material which is to define the support material is formed into a desired shape by a suitable method, for example moulding, machining of a blank, extrusion or the like. Then, the layer of bio-compatible material is formed on the outside of the support material. For example, a polymeric material which includes said copolymer may be contacted with said support material and caused to bond thereto. Thereafter, optionally, said copolymer may be treated, for example to functionalise it and/or associate bio-compatible moieties with it.

Said support material suitably has a tensile strength (according to ISO R527) of at least 80, preferably at least 90, especially at least 95 MPa. The tensile strength may be less than 360, suitably less than 250, preferably less than 140 MPa. It preferably has an elongate at break (according to ISO R527) of at least 40, preferably at least 50%. It preferably has a tensile

modulus (according to ISO R527) of greater than 2.5, preferably greater than 3, especially greater than 3.5 GPa. The tensile modulus may be less than 40, suitably less than 30, preferably less than 20, more preferably less than 10 GPa. It preferably has a flexural strength (according to ASTM D695) of at least 100, more preferably at least 110, especially at least 115 MPa. The flexural strength may be less than 650, preferably less than 400, more preferably less than 260, especially less than 200 MPa. It preferably has a flexural modulus (according to ISO R178) of at least 3, preferably at least 3.5, especially at least 4 GPa. The flexural modulus may be less than 60, suitably less than 25, preferably less than 20, especially less than 10 GPa. Advantageously, the aforementioned properties can be adjusted by appropriate selection of polymers and/or any reinforcement means included in said support material to suit particular applications. For example, a continuous carbon fibre polyetheretherketone may typically have a tensile strength of about 350 MPa, a tensile modulus of 36 GPa, an elongation of 2%, a flexural modulus of 50 GPa and a flexural strength of 620 MPa. A polyaryletherketone with 30% of high performance fibres may typically have a tensile strength of 224 MPa, a tensile modulus of 13 GPa, a tensile elongation of 2%, a flexural modulus of 20 GPa and a flexural strength of 250 MPa.

The invention extends to a method of making a medical device or part thereof, the method comprising: forming a material into a shape which represents or is a precursor of a device for use in medical applications wherein said material comprises a polymer; and treating material in said shape in order to define a layer on the outside of

said shape, wherein said layer includes a bio-compatible polymeric material as described according to said first aspect.

The invention further extends to a device for use in medical applications, wherein said device comprises a bio-compatible polymeric material as described in any statement herein.

Said device suitably includes a support material and a bio-compatible polymeric material on the outside thereof.

Said device is preferably a prosthetic device, for example an implant such as an orthopaedic, dental or maxillofacial implant or a component thereof; or a device, for example a catheter, which is arranged to be temporarily associated with a human or animal body. Said device is preferably a prosthetic device as described. An orthopaedic device may be an implant for a body joint, for example a hip or knee joint or spine fusion device.

A said device may include a part or parts made out of said bio-compatible polymeric material and a part or parts made out of other materials. Suitably, however, said device includes at least 50wt%, preferably at least 65wt%, more preferably at least 80wt%, especially at least 95wt% of said bio-compatible polymeric material. In some embodiments said device may consist essential of said bio-compatible polymeric material.

The invention extends to a method of making a medical device or part thereof, the method including the step of forming a layer (hereinafter an "X-ray contrast layer") on

the outside of a support material, wherein said layer includes an X-ray contrast medium.

Said X-ray contrast layer may have any feature of a layer which includes a said bio-compatible polymeric material described herein. Said support material may have any feature of a said support material described in any statement herein. Preferably said support material includes a lower amount of X-ray contrast medium than said X-ray contrast layer. Preferably, said support material includes substantially no X-ray contrast medium.

Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described by way of example.

The following materials are referred to herein:

PEN-polyethernitrile;
PDMS-polydimethylsiloxane;
PEKmK-polyetherketonemetaketone
PEKEI-polyetherketoneetherimide

Copolymers prepared as described in Examples I to V may be as follows:

<u>Example I</u> - The copolymers B units contain chemical moieties that allow efficient and cost effective

attachment of molecules that have enhanced biocompatability / bio-activity.

<u>Example II</u> - The copolymer B units already contain moieties that have enhanced biocompatability / bio-activity.

<u>Example III</u> - The copolymer contains amorphous polyaryletherketone, C units that are either dispersed throughout the bulk of the material or in phase domains. The amorphous units allow efficient and cost effective attachment of molecules that enhance biological activity or biocompatability.

<u>Example IV</u> - The copolymer contains A, B and C units that are either dispersed throughout the bulk of the material or in phase domains. The B units can give the benefits described for Example I and II combined with the added functionality described in Example III or the ability to add a second biologically functional molecule (or attachment species) to amorphous units.

<u>Example (V)</u> - A copolymer of A and B units blended with a copolymer of A and C units or A homopolymer. The copolymer of A and B units will give the advantages described for Examples I and II and in some embodiments the copolymer will be sufficiently dissimilar to that constructed from A and C units (the other blend constituent) that it will phase separate and be prevalent on the surface. The copolymer of A and C units will have the advantage described in Example III.

Example Ia Preparation of polyetheretherketone/PEN copolymer

A 700ml, flanged flask fitted with a ground glass Quickfit lid, stirrer/stirrer guide, nitrogen inlet and a thermocouple was charged with 4,4'-difluorobenzophenone (46.80g, 0.2145 mole), 2,6-difluorobenzonitrile (6.21g, 0.09 mole), hydroquinone (33.03g, 0.3 mole) and diphenysulphone (180.0g) and purged with nitrogen for over 1 hour. The contents were then heated under a nitrogen blanket to between 140 and 150°C to form an almost colourless solution. While maintaining a nitrogen blanket, dried sodium carbonate (31.80g, 0.30 mole) and potassium carbonate (0.84g, 0.006 mole) was added. The temperature was raised to 175°C, held for 60 min; heated to 200 °C, held for 30mins; heated to 250°C, held for 30 mins; heated to 300°C and held for 120 mins.

The reaction mixture was allowed to cool, milled and washed with acetone and water. The resulting polymer was dried in an air oven at 120°C. The polymer had an IV of 1.15 and a Melt Viscosity (MV) of 0.37kNsm^{-2} measured at 400°C on a ram extruder at a shear rate of 1000 s^{-1}. Tg = 145°C and Tm = 344°C.

Example Ib Hydrolysis of polyetheretherketone/PEN Copolymer

A film of the polymer from Example Ia 5cm x 2cm x 120μm was prepared by compression moulding at 400°C for 5 - 10 minutes between metal plates using a Moore Laboratory hot press. The film was placed in a 250ml round bottomed flask fitted with a reflux condenser. To the flask was

added 80ml of a 30% aqueous sodium hydroxide and 15ml of ethanol in order to facilitate complete hydrolysis of the nitrile to the carboxylic acid. The solution was heated to reflux for 12-24 hours in order to ensure complete hydrolysis. The solution was cooled and the film removed and placed in a solution of glacial acetic acid followed by washing with 2M HCl and distilled water. The sample was dried at room temperature overnight.

Example Ic Reaction of surface modified polyetheretherketone/PEN containing carboxylic acid groups with the peptide GRGDS

The surface modified polyetheretherketone/PEN of Example Ib was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide)(0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino) ethanesulphonic acid) (40ml). The sample of polyetheretherketone/PEN was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS(160mg) in phosphate-buffered saline solution (40ml) (Na_2HPO_4, 1.15g; KH_2PO_4, 0.2g; NaCl. 8g; KCl, 0.2g; $MgCl_2$, 0.1g; $CaCl_2$. 0.1g in 1 Litre of distilled water). The functionalised polyetheretherketone/PEN was washed successively with phosphate buffer and distilled water.

Example IIa Preparation of hydroxy-terminated polyetheretherketone

A 700ml, flanged flask fitted with a ground glass Quickfit lid, stirrer/stirrer guide, nitrogen inlet and a thermocouple was charged with 4,4'-difluorobenzophenone (65.46g, 0.30 mole), hydroquinone (34.02g, 0.309 mole) and diphenysulphone (180.0g) and purged with nitrogen for over 1 hour. The contents were then heated under a nitrogen blanket to between 140 and 150°C to form an almost colourless solution. While maintaining a nitrogen blanket, dried sodium carbonate (31.80g, 0.30 mole) and potassium carbonate (0.84g, 0.006 mole) was added. The temperature was raised to 175°C, held for 60 min; heated to 200 °C, held for 30mins; heated to 250°C, held for 30 mins; heated to 300°C and held for 120 mins.

The reaction mixture was allowed to cool, milled and washed with acetone and water. The resulting polymer was dried in an air oven at 120°C. The polymer had an IV of 0.41 and a Mn of 5000. Tg = 142°C and Tm = 342°C.

Example IIb Preparation of polyetheretherketone-PDMS Block Copolymer

A thoroughly dried 700ml flanged flask fitted with a ground glass Quickfit lid, stirrer/stirrer guide, nitrogen inlet and outlet and a thermocouple was charged with the polymer of Example IIa (30.0g, 0.006 mole) and 1-chloronaphthalene (450ml), heated to 150°C and purged with nitrogen for 1 hour. The contents were heated under a nitrogen blanket to 240°C then a solution of bisdimethylamine-terminated polydimethylsiloxane (Mn 4800) (29.3g, 0.0061 mole) in 1-chloronaphthalene (50ml) was added over a period of 2 hours, while maintaining a

nitrogen blanket. The temperature was held at 240°C for 90 mins after the addition was complete.

The reaction mixture was allowed to cool to room temperature. The product was precipitated by pouring the reaction mixture into methanol (2.5 litres), recovered by filtration and dried under vacuum at 80°C for 16 hours.

The overall molar percentage of copolymer units, the nature of the units and the block size determines the ~~resultant morphology of the bulk material and~~ the crystallinity in the polyketone phase. Discrete phase domains of B units have been measured on a melt processed surface between 0.5 and 400 μm.

Example IIIa **Preparation of PEKmK Oligomer**

A 1 litre round-bottomed flask fitted with a stirrer/stirrer guide, a solids addition funnel, nitrogen inlet and outlet and a thermocouple was charged with 1,2-dichloroethane (350ml), 3-fluorobenzoyl chloride (42.5g, 0.268 mole), diphenylether (68.08g, 0.4 mole) and isophthaloyl chloride (54.4g, 0.268 mole). The additional funnel was charged with aluminium chloride (150.08g, 1.126 mole) and added gradually to the solution, under an atmosphere of nitrogen, so the temperature was maintained at 5°C. The mixture was allowed to warm up to room temperature, held for 1 hour, heated to 75°C and held for 5 hours. The reaction mixture was homogeneous and viscous. It was allowed to cool to room temperature, then poured into cold, dilute hydrochloric acid (1 litre). The suspension was distilled to remove 1,2-dichloroethane. The crude product was recovered by filtration, washed with

methanol, deionised water until the washings were neutral, then finally with methanol and dried at 50°C under vacuum.

Example IIIb Preparation of PEKmK/polyetheretherketone Block Copolymer

A 700ml flanged flask fitted with a ground glass Quickfit lid, stirrer/stirrer guide, a nitrogen inlet and outlet and a thermocouple was charged with the PEKmK oligomer of Example Ia (10.66g, 0.016 mole), 4,4'-difluorobenzophenone (62.96g, 0.2885 mole), hydroquinone (33.03g, 0.30 mole) and diphenysulphone (180.0g) and purged with nitrogen for over 1 hour. The contents were then heated under a nitrogen blanket to between 140 and 150°C to form an almost colourless solution. While maintaining a nitrogen blanket, dried sodium carbonate (31.80g, 0.30 mole) and potassium carbonate (0.84g, 0.006 mole) was added. The temperature was raised to 175°C, held for 60 min; heated to 200 °C, held for 30mins; heated to 250°C, held for 30 mins; heated to 300°C and held for 120 mins.

The reaction mixture was allowed to cool, milled and washed with acetone and water. The resulting polymer was dried in an air oven at 120°C. The polymer had Inherent Viscosity (IV) of 1.1. IV is measured at 25°C on a solution of polymer in concentrated sulphuric acid of density 1.84gcm^3, said solution containing 0.1g of polymer per 100cm^3 of solution. A Melt Viscosity (MV) of 0.35kNsm^{-2} measured at 400°C on a ram extruder at a shear rate of 1000 s^{-1}. Tg = 145°C and Tm = 344°C.

Example IIIc Modification of PEKmK/polyetheretherketone Block Copolymer

To a three necked round bottomed flask equipped with a magnetic stirring bar and nitrogen inlet was added 4-bromobenzonitrile (3.0g, 16.50mmol). To this solution was added (10.3ml, 16.50mmol) of 1.6M n-butyl lithium at -78°C. The reaction solution was then stirred at -78°C for 1h. The reaction solution was transferred via cannulae to a test tube containing PEKmK/polyetheretherketone film of Example Ib (1cm x 5cm x 120cm) under a nitrogen atmosphere. The solution was then allowed to warm to room temperature and stirred for a further 24 hours. The films were then removed and washed with isopropanol (3 x 50ml), methanol (3 x 50ml) and acetone (2 x 50ml) before being dried at room temperature for 24h.

The dried film was placed in a 250ml round bottomed flask fitted with a reflux condenser. To the flask was added 80ml of a 10% aqueous sodium hydroxide and 15ml of ethanol in order to facilitate complete hydrolysis of the nitrile to the carboxylic acid. The solution was heated to reflux for 12-24 hours in order to ensure complete hydrolysis. The solution was cooled and the film removed and placed in a solution of glacial acetic acid followed by washing with 2M HCl and distilled water. The sample was dried at room temperature overnight.

Example IIId Reaction of surface modified PEKmK/polyetheretherketone containing carboxylic acid groups with the peptide GRGDS

The surface modified PEKmK/polyetheretherketone of Example IIIc was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide)(0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino) ethanesulphonic acid) (40ml). The sample of PEKmK/polyetheretherketone was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS(160mg) in phosphate-buffered saline solution (40ml) (Na_2HPO_4, 1.15g; KH_2PO_4, 0.2g; NaCl. 8g; KCl, 0.2g; $MgCl_2$, 0.1g; $CaCl_2$. 0.1g in 1 Litre of distilled water). The functionalised PEKmK/polyetheretherketone was washed successively with phosphate buffer and distilled water.

Example IVa Preparation of N,N′-bis(4-phenoxy phenyl)-3,3′,4,4′-diphenylhexafluoroisopropylidene tetracarboxylic di-imide

4-Phenoxyaniline (37.97g, 0.205 mole), 4,4′-(hexafluoroisopropylidene)diphthalic anhydride(3,3′,4,4′-diphenylhexafluoroisopropylidene dianhydride) (44.4g, 0.10 mole), dimethylacetamide (250ml) and xylene (40ml) were charged to a 1 litre, 3-necked, round-bottomed flask, fitted with a mechanical stirrer/stirrer guide, nitrogen inlet and outlet, a thermocouple and a Dean and Stark head. The mixture was heated to reflux with stirring and maintained at that temperature until all the water had been removed. The reaction mixture was allowed to cool to room temperature, poured into 1 litre of methanol,

filtered, washed with methanol and dried under vacuum at 90°C for 16 hours.

Example IVb Preparation of N,N'-bis(4-fluorobenzoyl)-(4-phenoxyphenyl)-3,3',4,4'-diphenylhexa-fluoroisopropylidene tetracarboxylic di-imide

A 1 litre round-bottomed flask fitted with a stirrer/stirrer guide, a solids addition funnel, nitrogen inlet and outlet, a thermocouple and a reflux condenser was charged with N,N'-bis(4-phenoxyphenyl)-3,3',4,4'-diphenylhexafluoroisopropylidenetetracarboxylic diimide (58.2g, 0.075 mole), 4-fluorobenzoylchloride (24.12g, 0.1512 mole), and 1,2-dichloroethane (375ml). The additional funnel was charged with aluminium chloride (225.12g, 1.689 mole) and added gradually to the stirred solution, under an atmosphere of nitrogen, so the temperature was maintained at 5°C. The mixture was allowed to warm up to room temperature, held at room temperature for 1 hour, heated to 75°C and held for 5 hours. The reaction mixture was homogeneous and viscous. It was allowed to cool to room temperature, then poured into cold, dilute hydrochloric acid (1l). The suspension was distilled to remove 1,2-dichloroethane. The crude product was recovered by filtration, washed with methanol, deionised water until the washings were neutral, then finally with methanol and dried at 50°C under vacuum. Recrystallised from dimethylacetamide (Yield 74%)

Example IVc Preparation of polyetheretherketone/PEKEI copolymers

A 700ml flanged flask fitted with a ground glass Quickfit lid, stirrer/stirrer guide, a nitrogen inlet and outlet and a thermocouple was charged with the product from Example IVb (26.97g, 0.03 mole), 4,4'-difluorobenzophenone (59.90g, 0.2745 mole), hydroquinone (33.03g, 0.30 mole) and diphenysulphone (180.0g) and purged with nitrogen for over 1 hour. The contents were then heated under a nitrogen blanket to between 140 and 150°C to form an almost colourless solution. While maintaining a nitrogen blanket, dried sodium carbonate (31.80g, 0.30 mole) and potassium carbonate (0.84g, 0.006 mole) was added. The temperature was raised to 175°C, held for 60 min; heated to 200 °C, held for 30mins; heated to 250°C, held for 30 mins; heated to 300°C and held for 120 mins.

The reaction mixture was allowed to cool, milled and washed with acetone and water. The resulting polymer was dried in an air oven at 120°C. The polymer had Inherent Viscosity (IV) of 1.21. IV is measured at 25°C on a solution of polymer in concentrated sulphuric acid of density 1.84gcm^3, said solution containing 0.1g of polymer per 100cm^3 of solution. A Melt Viscosity (MV) of 0.43kNsm^{-2} measured at 400°C on a ram extruder at a shear rate of 1000 s^{-1}.

Example IVd **Modification of polyetheretherketone/PEKEI Copolymer**

A dried film of the copolymer from Example IVd (5cm x 1 cm x 120μm) was placed in a 250ml round bottomed flask fitted with a reflux condenser. To the flask was added 80ml of a 30% aqueous sodium hydroxide and 15ml of ethanol

in order to facilitate the hydrolysis of the imide to the amic acid. The solution was heated to reflux for 24 hours. The solution was cooled and the film removed and placed in a solution of glacial acetic acid followed by washing with 2M HCl and distilled water. The sample was dried at room temperature overnight.

Example IVe Reaction of surface modified polyetheretherketone/PEKEI copolymer containing carboxylic acid groups with the peptide GRGDS

The surface modified polyetheretherketone/PEKEI from Example IVd was stirred at 10°C for 1 hr under an atmosphere of nitrogen in an aqueous solution of the water soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide)(0.4g) dissolved in buffer at pH 4.5 (0.1M 2-(N-morpholino) ethanesulphonic acid) (40ml). The sample of polyetheretherketone/PEKEI was removed and washed with buffer solution.

The sample was stirred at 20°C for 24 hr under an atmosphere of nitrogen in a solution of the peptide GRGDS(160mg) in phosphate-buffered saline solution (40ml) (Na_2HPO_4, 1.15g; KH_2PO_4, 0.2g; NaCl. 8g; KCl, 0.2g; $MgCl_2$, 0.1g; $CaCl_2$. 0.1g in 1 Litre of distilled water). The functionalised polyetheretherketone/PEKEI was washed successively with phosphate buffer and distilled water.

Example Va The blend of polyetheretherketone/PEN copolymer with polyaryletheretherketone

5 kg of the copolymer polyetheretherketone/PEN were prepared as described in Example Ia. These materials were

in the form of a microporous polymeric flake. The flake was feed into the 32 mm cm single screw extruder to form a lace of densified polymer. The extruded lace was cooled in air post extruder and pellitised producing pellets of approximately 3 mm length and 2.5 mm diameter. These pellets were placed in clean aluminium trays at a depth of approximately 2.5 cm. The trays were placed in an air-circulating oven at 130 °C for 5 hours.

After that time the polyetheretherketone/PEN pellets were placed in a Marion Tumble blender along with an equivalent weight (4.01 kg) of polyaryletheretherketone 381G produced by Victrex plc. The system was agitated for 30 minutes to produce a premix of similar shaped pellets or similar density.

The resultant mixture was fed using a Brabender loss in weight feeder into a 25 mm KrausMaffei twin screw extruder. The blended polymer was then extruded to form a lace that was cooled and pelletised as previously detailed.

The polymer blend was then injection moulded using a Neggri Bossi 100 tonnes clamping force moulder to form 150 mm x 150 mm x 6 mm plaques. These plaques were then treated in methods analogous to examples Ib and Ic.

Example Vb The blend of PEKmK/polyetheretherketone Block Copolymer with polyetheretherketone/PEN copolymer

Example Vb is substantially similar to example Va except for the following; the PEKmK/polyetheretherketone block copolymer was prepared as described in example IIIb

and supplied as a micorporous flake. This flake was denisfied using a 32 mm single screw extruder as previously discussed. These pellets were dried and tumbled blended with an equal weight of the densified polyetheretherketone/PEN copolymer. The premixture was then blended using a twin screw extruder and injection moulded as previously discussed. The plaques produced were treated in methods analogous to examples IB and IC.

Example Vc The blend of PEKmK/polyetheretherketone Block Copolymer with polyaryletheretherketone

Example Vc is substantially similar to example Vb except for the following; the PEKmK/polyetheretherketone block copolymer was prepared as described in example IIIb and supplied as a micorporous flake. This flake was denisfied using a 32 mm single screw extruder as previously discussed. These pellets were dried and tumbled blended with an equal weight of the densified polyaryletheretherketone 381G supplied by Victrex plc. The premixture was then blended using a twin screw extruder and injection moulded as previously discussed.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or

process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

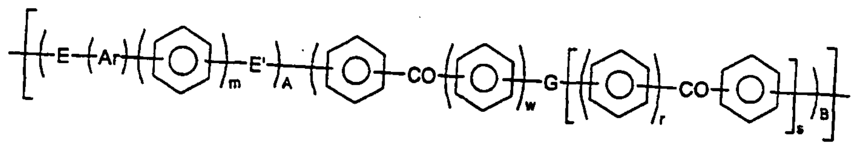
1. A bio-compatible polymeric material for use in medical applications, wherein said material comprises a copolymer comprising a unit A in combination with a unit B and/or a unit C, wherein bio-compatible moieties are associated with said copolymer and A represents a semi-crystalline polyaryletherketone moiety, B represents a unit which is incompatible with unit A and C represents an amorphous polyaryletherketone or polyarylethersulphone unit.

2. A polymeric material according to claim 1, wherein B units are sufficiently chemically dissimilar to A units, such that blocks of B units are adapted to selectively aggregate when a copolymer comprising A and B units is cooled from a melt.

3. A polymeric material according to claim 1 or claim 2, wherein bio-compatible moieties are associated with at least one of either unit B or unit C of said copolymer.

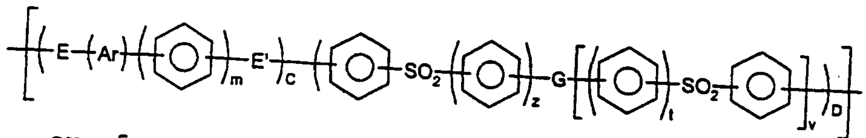
4. A polymeric material according to any preceding claim, wherein unit A includes aromatic group containing moieties linked by -CO- and/or -Q- groups, wherein -Q- is an oxygen or sulphur atom.

5. A polymeric material according to any preceding claim, wherein unit A includes a first unit which is of general formula



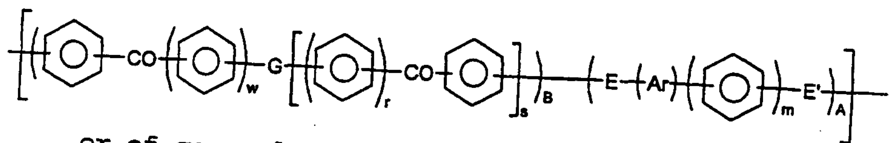
IV

or of general formula



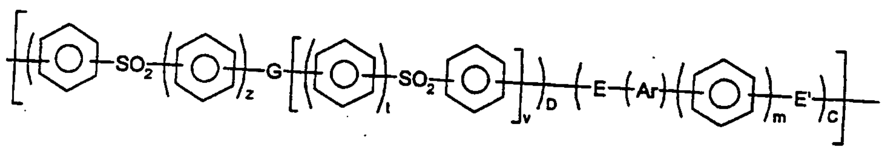
V

or of general formula



IV*

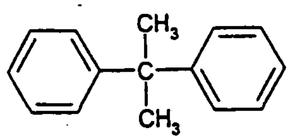
or of general formula



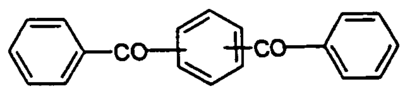
V*

provided said unit is semi-crystalline, wherein the phenyl moieties in units IV, IV*, V and V* are independently optionally substituted, wherein m,r,s,t,v,w and z independently represent zero or a positive integer, E and E' independently represent an oxygen or a sulphur atom or a direct link, G represents an oxygen or sulphur atom, a direct link or a -O-Ph-O- moiety where Ph represents a phenyl group and Ar is selected from one of the following moieties (i)*, (i)**, and (i) to (x) which is bonded via one or more of its phenyl moieties to adjacent moieties

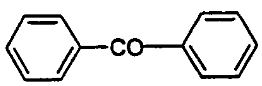
(i)**



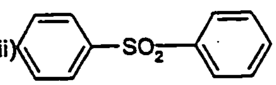
(i)*



(i)



(ii)



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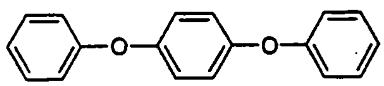

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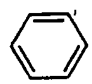
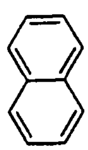
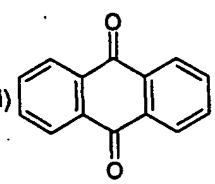


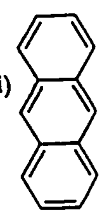
(v)



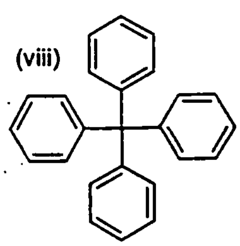
(vi)



(vii)



(viii)



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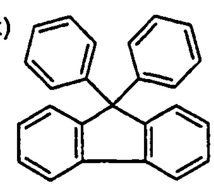
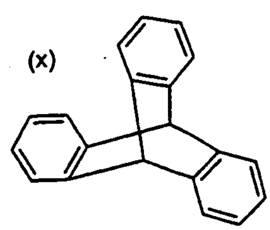


(x)



6. A polymeric material according to any preceding claim, wherein unit A includes only unsubstituted phenyl moieties ether moieties and ketone moieties.

7. A polymeric material according to any preceding claim, wherein unit A is selected from polyetheretherketone, polyetherketone, polyetherketoneketone, polyetherketoneetherketoneketone and polyetheretherketoneketone.

8. A polymeric material according to any preceding claim, wherein unit A is selected from polyetheretherketone and polyetherketone.

9. A polymeric material according to any preceding claim, wherein unit A comprises polyetheretherketone.

10. A polymeric material according to any preceding claim, wherein unit B does not include any ether moieties in its backbone.

11. A polymeric material according to any preceding claim, wherein unit B does not include any ketone moieties in its backbone.

12. A polymeric material according to any preceding claim, wherein unit B does not include any phenyl moieties in its backbone.

13. A polymeric material according to any preceding claim, wherein unit B is a dimethylsiloxane.

14. A polymeric material according to any preceding claim, wherein unit C includes aromatic group containing moieties linked by $-SO_2-$ and/or $-CO-$ and/or $-Q-$ groups, wherein Q is an oxygen or sulphur atom, provided that said third unit includes a means to render it amorphous and/or not

crystallisable with polyarylether ketones or polyarylthioether ketones and/or not crystallisable with unit A described.

15. A polymeric material according to any preceding claim, wherein said unit C comprises a unit which is of formula -Q-Z-Q- wherein Z represents said aromatic group containing moiety, wherein said unit is not symmetrical about an imaginary line which passes through the two -Q- moieties provided that said unit is not dihydroxybenzophenone substituted by groups -Q- at the 4- and 4'- positions.

16. A polymeric material according to any preceding claim, wherein an end unit of said copolymer is an A unit.

17. A polymeric material according to any preceding claim, wherein the sum of the chain length(s) of A units in said copolymer is greater than the chain length(s) of B units in the polymer.

18. A polymeric material according to any preceding claim, wherein the sum of the chain length(s) of A units in said copolymer is greater than the sum of the chain length(s) of C units in said polymer.

19. A method of preparing a bio-compatible polymeric material, the method including the step of preparing a copolymer comprising a unit A in combination with a unit B and/or with a unit C and optionally including the step of associating a bio-compatible moiety with the copolymer or, when said optional step is not undertaken, selecting at least one unit B or C which is itself bio-compatible,

wherein A represents a semi-crystalline polyaryletherketone moiety and B represents a unit which is incompatible with unit A and C represents an amorphous polyaryletherketone or polyarylethersulphone unit.

20. A method according to claim 19, wherein the copolymer made in the method (prior to any optional step of associating bio-compatible moieties with the polymer) is thermally stable at at least 350°C.

21. A method according to claim 19 or claim 20, wherein units B and/or C in the bio-compatible polymeric material include associated bio-compatible moieties or are themselves bio-compatible to a greater extent than units A.

22. A method according to any of claims 19 to 21, wherein the method comprises one of the following:

(a) the preparation of a copolymer comprising units A and B wherein unit B includes pendent moieties with associated bio-compatible moieties;

(b) the preparation of a copolymer comprising units A and B wherein unit B is itself bio-compatible in that it has a higher inherent bio-compatibility compared to unit A;

(c) the preparation of a copolymer comprising units A and C wherein unit C is more easily functionalised compared to unit A so that bio-compatible moieties can be associated with functionalised unit C;

(d) the preparation of a copolymer comprising units A, B and C wherein units B and/or C provide bio-compatibility;

(e) the preparation of a first copolymer which comprises units A and B and a second copolymer which comprises units A and C.

23. A method according to any of claims 19 to 22, which includes providing said copolymer as part of a solid material.

24. A method according to claim 23, wherein a polymeric material which includes said copolymer is formed into a solid.

25. A method according to any of claims 19 to 24, wherein the copolymer and/or the polymeric material is such that the concentration of units B and/or C at the surface is greater than in the bulk.

26. A method of making a medical device or part thereof, the method including the step of forming a layer of a bio-compatible polymeric material on the outside of a support material, wherein said bio-compatible polymeric material is as described according to any of claims 1 to 18 or is made as described in any of claims 19 to 25.

27. A method according to claim 26, wherein said support material comprises the same copolymer which is included in the layer of bio-compatible material before any subsequent treatment to associate it with bio-compatible moieties or is made out of a material which is different to that of the material of the layer of bio-compatible material

before any subsequent treatment of said layer of bio-compatible material to associate it with bio-compatible moieties.

28. A method of making a medical device or part thereof, the method comprising: forming a material into a shape which represents or is a precursor of a device or part thereof for use in medical applications wherein said material comprises a polymer; and treating material in said shape in order to define a layer on the outside of said shape, wherein said layer includes a bio-compatible polymeric material as described in any of claims 1 to 18.

29. A device for use in medical applications, wherein said device comprises a bio-compatible polymeric material as described in any of claims 1 to 18.

30. A method of making a medical device or part thereof, the method including the step of forming a layer on the outside of a support material, wherein said layer includes an X-ray contrast medium.

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 01/02792

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L27/14 A61L31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L A61F A61M C08L C08G C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, COMPENDEX, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CORFIELD G C ET AL: "SYNTHESIS AND PROPERTIES OF POLYETHERETHERKETONE-POLYDIMETHYLSILOXANE BLOCK COPOLYMERS" JOURNAL OF POLYMER SCIENCE, POLYMER CHEMISTRY EDITION, JOHN WILEY AND SONS. NEW YORK, US, vol. 28, no. 10, 1 September 1990 (1990-09-01), pages 2821-2836, XP000167855 ISSN: 0887-624X abstract ---	1-29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	08/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muñoz, M

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RISCH B G ET AL: "Structure-property behaviour of poly(ether ether ketone)-polydimethylsiloxane block copolymers and their ketamine precursors" POLYMER, ELSEVIER SCIENCE PUBLISHERS B.V, GB, vol. 37, no. 7, 1 March 1996 (1996-03-01), pages 1229-1242, XP004069364 ISSN: 0032-3861 abstract	1-29
X	EP 0 659 389 A (SCHNEIDER EUROP AG) 28 June 1995 (1995-06-28) abstract	30
A	WO 92 07894 A (RAYCHEM LTD) 14 May 1992 (1992-05-14) claims	1-29
A	US 4 968 758 A (MATZNER MARKUS ET AL) 6 November 1990 (1990-11-06) column 1, line 7 - line 40	1-29
A	US 4 774 296 A (CLENDINNING ROBERT A ET AL) 27 September 1988 (1988-09-27) claims	1-29

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-29

   A biocompatible polymeric material based on a polyaryletherketone copolymer, a method of making such biocompatible copolymer.

2. Claim : 30

   A method of making a medical device, the method including the step of forming a layer, wherein said layer includes an X-ray contrast medium

Continuation of Box I.2

Present claims 1-21 relate to compounds defined by reference to a desirable characteristic or property, namely that the copolymer is associated with "biocompatible moieties" and that B represents a unit incompatible with A and C.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved, i.e. to have biocompatible moieties or to be incompatible with other polymers. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Moreover, claims 1-21 relate to extremly large number of possible copolymers while only a small proportion of these are supported within the meaning of Article 6 PCT or disclosed within the meaning of Article 5 PCT.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the copolymers disclosed in the examples namely: PEEK/PEN, PEEK/PDMS, PEKmK/PEEK, PEKEI/PEEK and blends thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/02792

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